Discovery of TMPRSS2 inhibitors from virtual screening as potential treatment of COVID-19

Xin Hu*, Jonathan H. Shrimp, Hui Guo, Miao Xu, Catherine Z. Chen, Wei Zhu, Alexey Zakharov, Sankalp Jain, Paul Shinn, Anton Simeonov, Matthew D. Hall, Min Shen*

National Center for Advancing Translational Sciences (NCATS), National Institutes of Health, 9800 Medical Center Drive, Rockville, MD, 20850, United States

Supplementary Information

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Figure S-1. TMPRSS2 structural model (blue) superimposed with template structure hepsin (magenta, PDB 1Z8G) and two related serine proteases Coagulation Factor Xa (brown, PDB 1KSN) and Urokinase (grey, PDB 1F92).

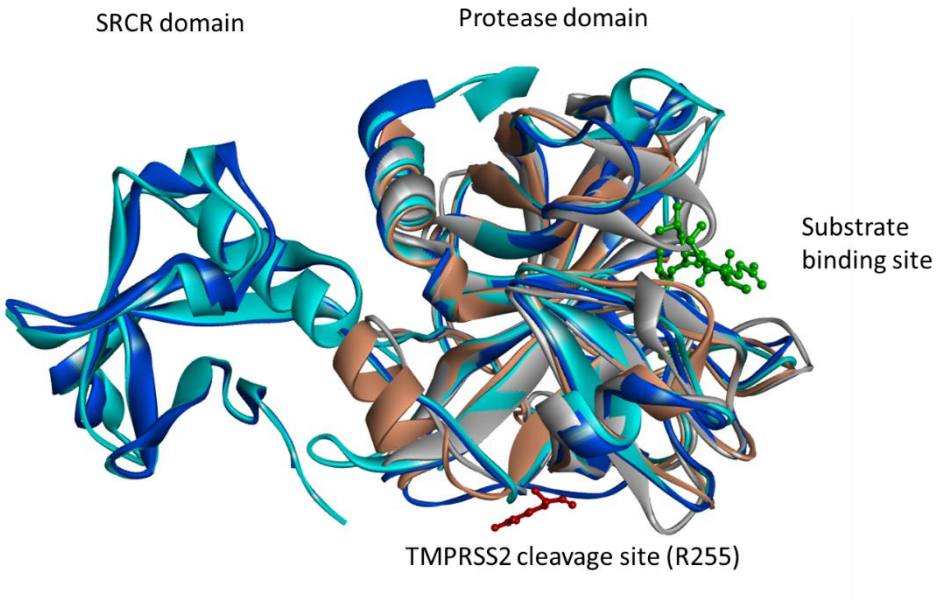


Figure S-2. RMSF plot of TMPRSS2 with the apo and inhibitor-bound complexes in the MD simulations.

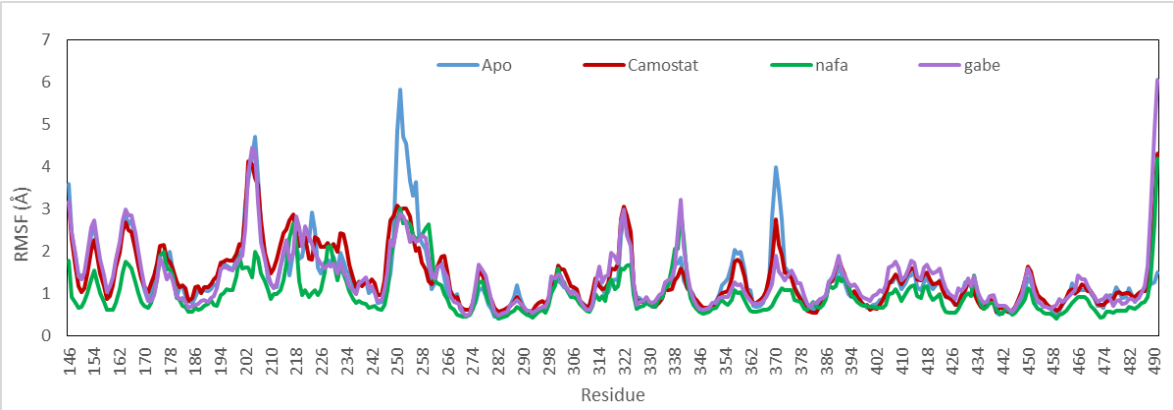
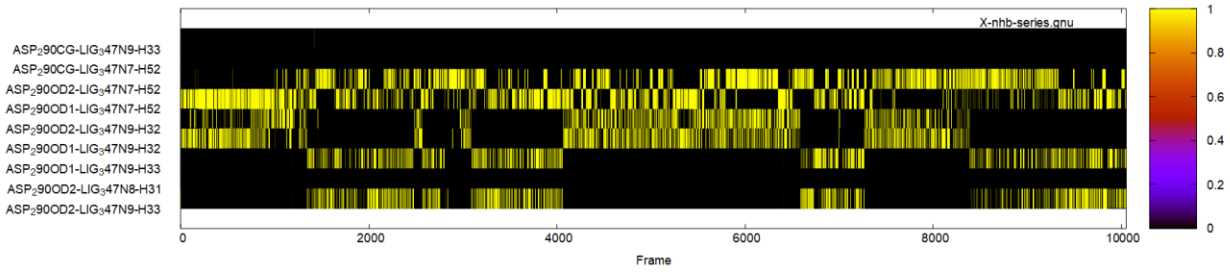
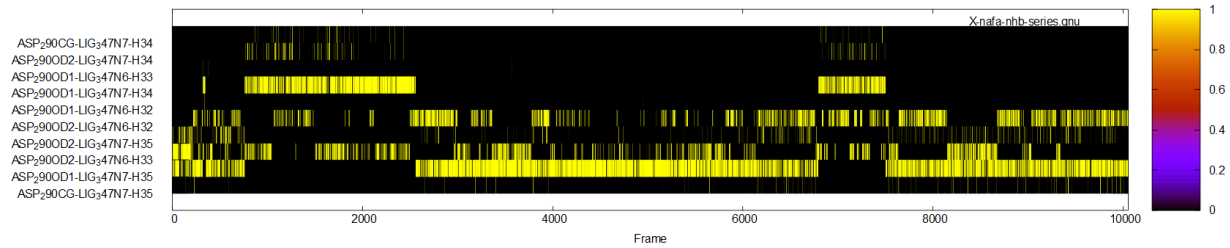


Figure S-3. Plot of H-bond interactions between the guanidinium head group of TMPRSS2 inhibitors bound and Asp239 in the 10-ns MD simulations.

Camostat



Nafamostat



Gabexate

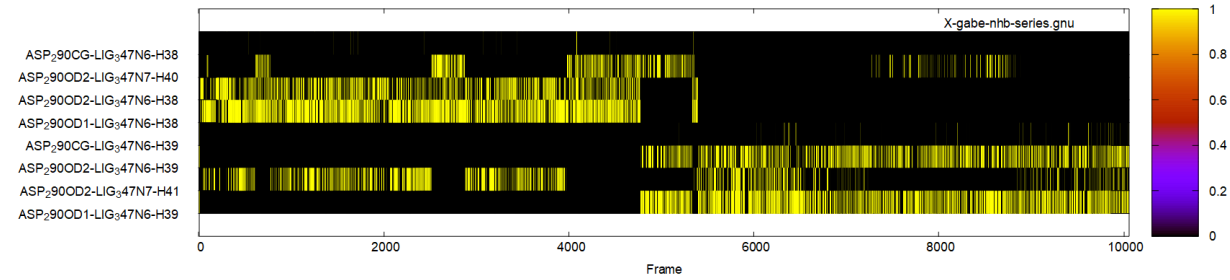


Figure S-4. Pharmacophore model used for TMPRSS2 virtual screening. The pharmacophore models were generated based on the predicted binding interactions of TMPRSS2 with inhibitor camostat (red), nafamostat (green) and gabexate (dark yellow) using MOE. Four pharmacophoric features were included: 1) an Don2 projected H-bond donor feature placed on the sidechain of Asp435 in the S1 pocket; 2) an Acc2 projected H-bond acceptor feature placed on the N atom of sidechain of Gln438; 3) an hydrophobic centroids Hyd feature matching hydrophobic interactions at the S1' hydrophobic region mainly formed by Val275, Val280, and Leu302; 4) an Don2 projected H-bond donor feature placed on the sidechain of Glu299.

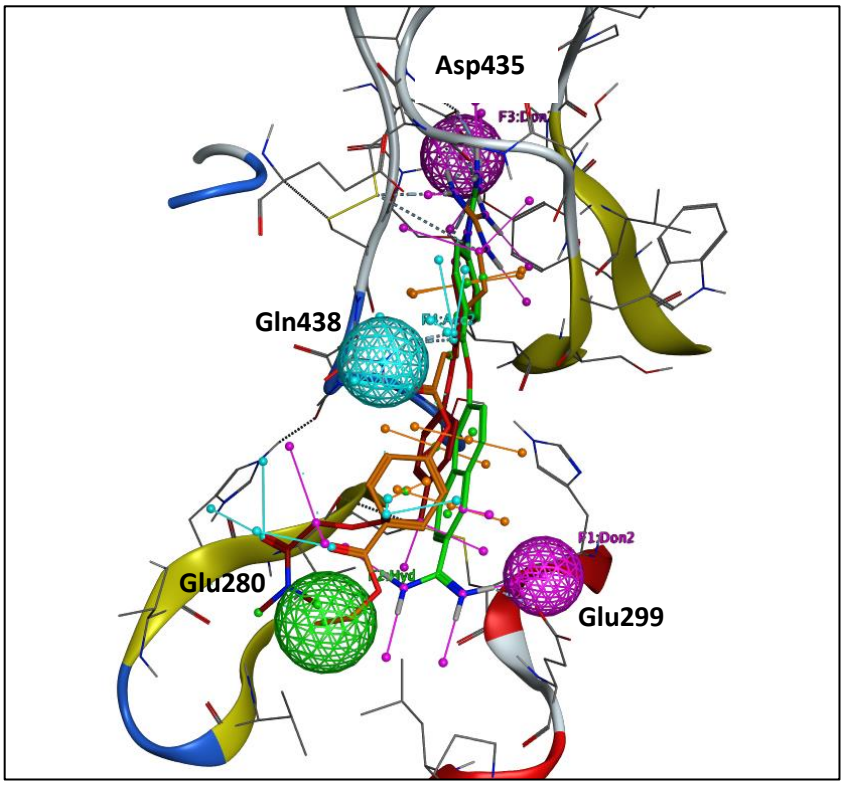


Figure S-5. Activities of identified inhibitors in the TMPRSS2 enzyme assay and counter screen.

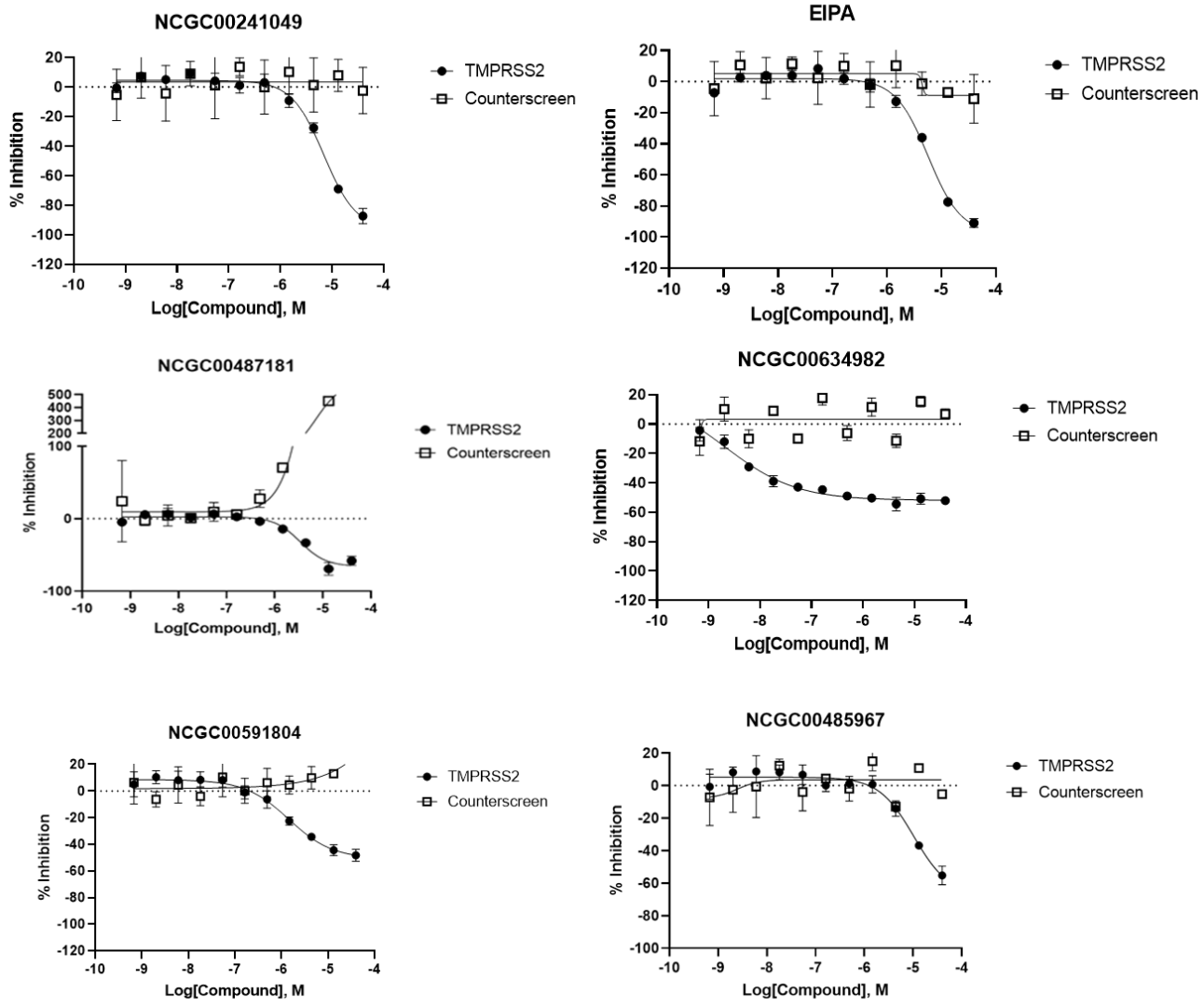


Figure S-6. Activities of TMPRSS2 inhibitors Avoralastat, PCI-27483 and Antipain in the SARS-COV-2 PP entry assay and counter screen.

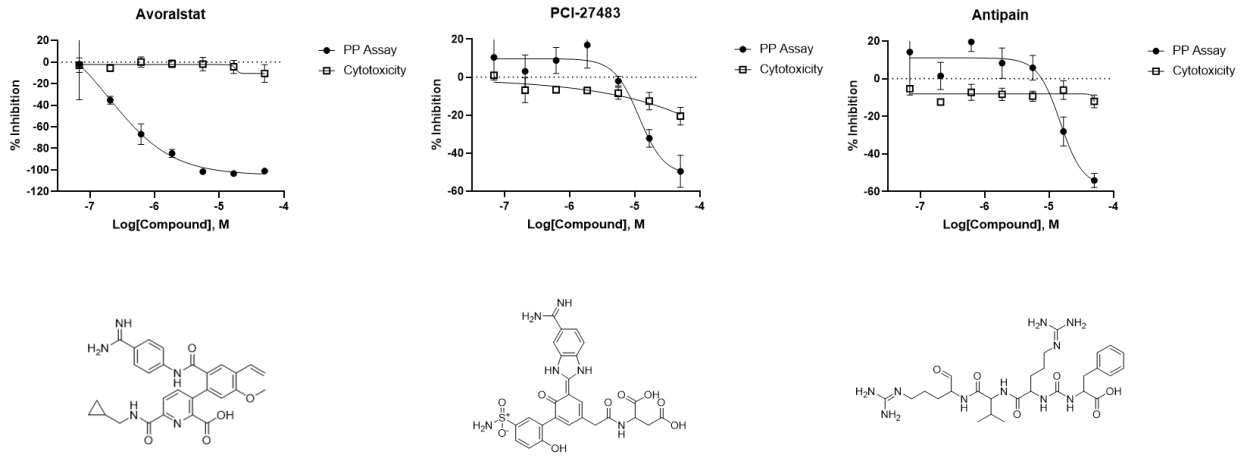


Figure S-7. Predicted binding models of TMPRSS2 inhibitors from VS. Protein surface is shown in hydrophobicity and small molecules are shown in sticks. Two binding models of otamixaban were predicted from docking analysis.

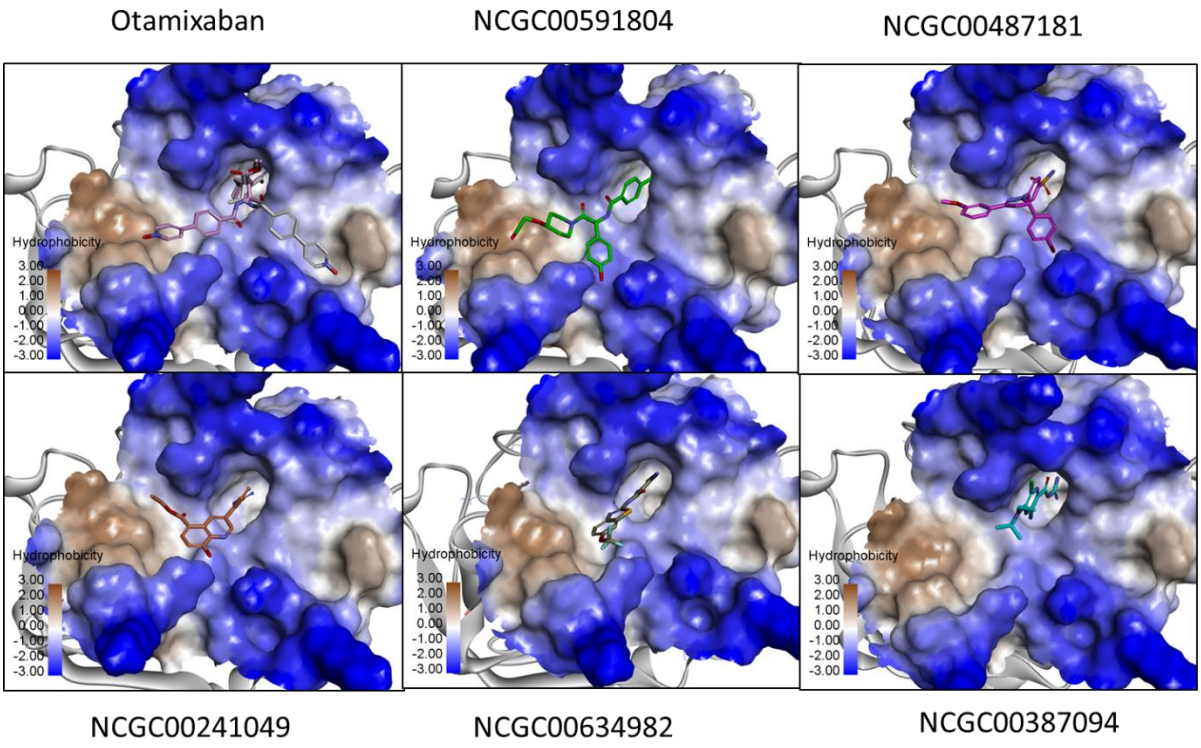
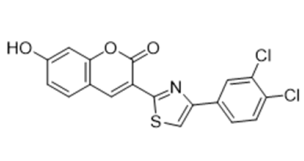
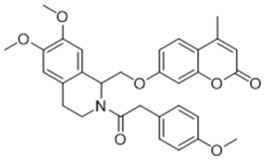


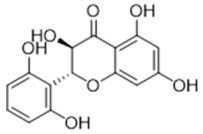
Figure S-8. Quinol-like hits identified from virtual screening and activities tested in the TMPRSS2 enzyme assay.



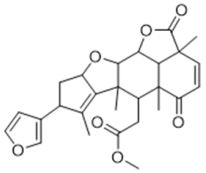
NCGC00138440
(1.96 uM, 46.7%)



NCGC00104913
(40uM, 87.6%)



NCGC00385208
(27.7uM, 40.9%)



NCGC00390383
(35 uM, 32.7%)

Table S-1. Chemical properties of TMPRSS2 inhibitors in this study.

NCGC ID	Name	MW	HB-Acc	HB-Don	LogP	TPSA
NCGC00160398	Nafamostat Mesylate	347.37	9	4	2.36	141.55
NCGC00167526	Camostat Mesylate	398.41	5	5	1.37	136.55
NCGC00025297	Gabexate mesylate	321.37	5	4	1.99	116.24
NCGC00378763	Otamixaban	446.50	5	4	1.52	132.47
NCGC00522442	UKI-1	613.81	5	5	5.03	147.63
NCGC00421880		701.30	7	4	7.73	110.51
NCGC00386945		457.57	6	4	3.91	97.62
NCGC00485967	CBB1007	534.61	9	6	-0.16	176.62
NCGC00591804		468.50	7	7	-0.50	170.61
NCGC00241049		335.36	6	3	3.14	111.03
NCGC00387094	EIPA	299.76	7	6	1.43	135.75
NCGC00487181	CID44216842	486.38	3	4	4.62	84.99
NCGC00634982		355.30	3	6	3.64	103.02
NCGC00138440		390.24	1	3	5.44	62.25
NCGC00385208		304.25	5	7	1.81	127.45
NCGC00104913		529.58	0	6	4.36	83.53
NCGC00390383	Nimbolide	466.52	0	4	3.11	92.04
NCGC00387860	PCI-27483	596.57	12	12	-2.02	282.49
NCGC00522636	Avoralstat	513.54	7	6	2.40	172.06
NCGC00390338	Antipain	604.70	15	10	-2.95	288.55